

YEAR IN CARDIOLOGY SERIES

The Year in Interventional Cardiology

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We hope this report will help highlight scientific papers published in the year 2005 that have focused on interventional cardiology (Table 1). In addition, we have included late-breaking trials presented at the American College of Cardiology, Transcatheter Cardiovascular Therapeutics, and American Heart Association Conferences. We hope that the paper will provide a broad overview of the field for general cardiologists and an organized outline for detailed study for those with a specific interest in interventional cardiology. Finally, we have asked the I2 Summit Steering Committee members to help us select the top ten articles of the year.

ACUTE MYOCARDIAL INFARCTION (AMI)

In 2005, most interest was focused on studies designed to evaluate the role of percutaneous coronary intervention (PCI) after initial treatment with thrombolytic therapy.

Rescue PCI for failed thrombolysis. Although PCI is widely accepted as the best initial treatment strategy for patients with AMI, there has been controversy about the benefit of PCI in patients with failed thrombolysis. In the previously reported Middlesbrough Early Revascularization to Limit Infarction (MERLIN) trial, PCI resulted in a modest reduction in ischemia-driven revascularization; however, stroke and transfusions were more common in the rescue PCI group, and there was no difference in mortality (1). Results of the larger Rescue Angioplasty versus Conservative Treatment or Repeat Thrombolysis (REACT) trial were published in 2005 (2). Patients with lack of ST-segment resolution 90 min after thrombolysis ($n = 427$) were randomized to three arms: rescue PCI, repeat thrombolysis using tissue-type plasminogen activator or reteplase, or conservative care. The primary end point of combined death, reinfarction, stroke, or severe heart failure within six months was significantly reduced in the rescue PCI arm (15.3%) compared with 31.0% in the repeat thrombolysis

arm, and 29.8% with conservative care ($p = 0.001$). This benefit was due to reduction in death, reinfarction, and heart failure. Moreover, significantly less ischemia-driven revascularization was required in the rescue PCI arm. These data suggest that patients with failed thrombolysis should undergo rescue stenting.

Immediate PCI after thrombolysis. Prior clinical guidelines discouraged routine angioplasty after thrombolysis because of historical (but outdated) studies suggesting an excess risk of complications in these patients. Since then, significant advances in mechanical and pharmacological therapy have occurred. In the Combined Angioplasty and Pharmacological Intervention versus Thrombolysis Alone in Acute Myocardial Infarction (CAPITAL AMI) study, tenecteplase plus immediate angioplasty was found to be superior to tenecteplase alone in 170 high-risk ST-segment elevation myocardial infarction (STEMI) patients (3). Major adverse cardiac events (MACE) were significantly reduced at six months in the tenecteplase-PCI group (11.6% vs. 24.4%, $p = 0.04$), largely due to reductions in recurrent unstable ischemia and reinfarction. There was no increase in the incidence of major bleeding. Thus, in the era of stents and newer antiplatelet agents, routine PCI after thrombolysis is not only safe, but improves outcomes and thus may be preferable to “watchful waiting.”

Among patients who are selected to undergo delayed coronary angiography and intervention after thrombolysis, early pre-treatment with clopidogrel appears to be beneficial. In the PCI-Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY) study, 1,863 patients underwent PCI two to eight days after thrombolysis for AMI (4). At 30 days, pre-treatment with clopidogrel not only reduced reinfarction and stroke before PCI, but improved the combined end point of cardiovascular death, myocardial infarction, or stroke after PCI (3.6% vs. 6.2%, $p = 0.008$). This difference was observed despite recommending a loading dose of open-label clopidogrel to be administered in the cath lab for placebo patients, and use of glycoprotein IIb/IIIa inhibitors at the operator's discretion.

Facilitated PCI. For patients with anticipated delay to PCI, there has been tremendous interest in using pharmacologic agents before PCI to achieve early infarct vessel patency and therefore improve clinical outcomes. However, results of the Assessment of the Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction

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Table 1. Glossary of Interventional Cardiology Trials Published or Presented in 2005

Acronym	Trial
AMISTAD-2	Acute Myocardial Infarction Study of Adenosine
ARMYDA-2	Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty
ARTS	Arterial Revascularization Therapies Study
ASPIRE	Arixtra Study in Percutaneous Coronary Intervention: a Randomized Evaluation
ASSENT-4	Assessment of the Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction
ASTAMI	Effects on left ventricular function by intracoronary injections of autologous mononuclear bone marrow cells in acute anterior wall myocardial infarction
BASKET	Basel Stent Kosten Effektivitäts Trial
BRAVE-2	Bavarian Reperfusion AlternatiVes Evaluation-2
CAPITAL AMI	Combined Angioplasty and Pharmacological Intervention versus Thrombolytics ALone in Acute Myocardial Infarction
CLEAR PLATELETS	Clopidogrel Loading with Eptifibatide to Arrest the Reactivity of Platelets
CREATE-ECLA	Clinical Trial of Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation-Estudios Cardiológicos Latinoamérica
CREST	Cilostazol for Restenosis Trial
DIABETES	Diabetes and Sirolimus-Eluting Stent
DIRECT	Direct myocardial revascularization In Regeneration of Endomyocardial Channels
DREAM	Dutch Randomized Endovascular Aneurysm Management
EASY	A prospective randomized trial of transradial PCI with bolus abciximab versus bolus abciximab plus infusion
EMERALD	Enhanced Myocardial Efficacy and Removal by Aspiration of Liberated Debris
ENDEAVOR-II	A prospective, randomized comparison of the ABT-578-coated Driver stent with a bare stent
ENDEAVOR-III	A prospective, randomized comparison of zotarolimus-eluting and sirolimus-eluting stents in patients with coronary artery disease
ERACI	Argentine randomized study: coronary angioplasty with stenting versus coronary bypass surgery in multivessel disease
EUROINJECT	Direct Intramyocardial Plasmid Vascular Endothelial Growth Factor-A ₁₆₀ Gene Therapy in Patients with Stable Severe Angina Pectoris
EVAR	Endovascular Aneurysm Repair
FIRSTLINE-AMI	Front-Integrated Revascularization and Stem Cell Liberation in Evolving Acute Myocardial Infarction by Granulocyte Colony-Stimulating Factor
ICTUS	Invasive versus Conservative Treatment in Unstable Coronary Syndromes
ISAR-CHOICE	Intracoronary Stenting and Antithrombotic Regimen: Choose between 3 high Oral doses for Immediate Clopidogrel Effect
ISAR-DIABETES	Intracoronary Stenting and Angiographic Results: Do Diabetic Patients Derive Similar Benefit from Paclitaxel-Eluting and Sirolimus-Eluting Stents
ISAR-DESIRE	Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for In-Stent Restenosis
ISAR-TEST	A prospective, randomized trial of the Yukon non-polymer-based rapamycin-coated stent and the polymer-based paclitaxel-eluting stent in patients with coronary artery disease
GIPS-2	Glucose-Insulin-Potassium study in patients with ST elevation myocardial infarction without signs of heart failure
JUMBO-TIMI 26	Joint Utilization of Medications to Block Platelets Optimally
JUPITER-2	A prospective randomized trial of a tacrolimus-eluting stent compared to a carbon-coated stent in patients with coronary artery disease
LE MANS	A prospective randomized trial of stent implantation vs bypass graft surgery in patients with left main coronary artery disease
PCI-CLARITY	PCI-Clopidogrel as Adjunctive Reperfusion Therapy
PREVENT-4	PRoject of Ex-Vivo Vein Graft ENgineering via Transfection
PRIDE	Protection During Saphenous Vein Graft Intervention to Prevent Distal Embolization
PRISON-II	A prospective randomized trial of sirolimus-eluting and bare metal stents in patients with chronic total occlusions
PROMISE	Protection Devices in PCI Treatment of Myocardial Infarction for Salvage of Endangered Myocardium
PROXIMAL	Proximal Protection During Saphenous Vein Graft Intervention Using the Proxis Embolic Protection System
REACT	Rescue Angioplasty versus Conservative Treatment or Repeat Thrombolysis
REALITY	Randomized multicenter head-to-head comparison of the sirolimus-eluting stent (Cypher) and the paclitaxel-eluting stent (Taxus)
REMEDIA	Randomized Evaluation of the Effect of Mechanical Reduction of Distal Embolization by Thrombus-Aspiration in Primary and Rescue Angioplasty
REPAIR AMI	Intracoronary infusion of bone marrow-derived progenitor cells in acute myocardial infarction: a randomized, double-blind, placebo-controlled multicenter trial
RESEARCH	Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital
REVIVAL-2	A prospective randomized, double-blind trial of granulocyte colony stimulating factor in patients with acute myocardial infarction
SCANDSTENT	Stenting of coronary arteries in non-Stress/Benestent disease
SENIOR-PAMI	A prospective randomized trial of primary angioplasty and thrombolytic therapy in elderly patients with acute myocardial infarction
SIRTAX	Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization
SISR	Sirolimus-eluting stent vs. Intravascular Brachytherapy in the Treatment of Patients with In-stent Restenotic Coronary Lesions

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Table 1 Continued

Acronym	Trial
SPIDER	Saphenous Vein Graft Protection In a Distal Embolic Protection Randomized Trial
STRATEGY	Single High Dose Bolus Tirofiban and Sirolimus Eluting Stent vs Abciximab and Bare Metal Stent in Myocardial Infarction
TAXi	A prospective randomized comparison between paclitaxel and sirolimus stents in the real world of interventional cardiology
TAXUS-V	Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease
TAXUS-VI	Prospective, multicenter, randomized trial of the polymer-based paclitaxel-eluting stent in patients with de novo lesions
TiNOX	Randomized comparison of a titanium-nitride-oxide-coated stent with a stainless steel stent for coronary revascularization
X AMINE ST	X-Sizer in AMI for Negligible Embolization and Optimal ST resolution

(ASSENT)-4 trial, presented at the European Society of Cardiology and American Heart Association, demonstrated that facilitated PCI with full-dose tenecteplase was harmful compared to primary PCI alone (5). In this trial 1,667 patients with STEMI <6 h from symptom onset with anticipated door-to-balloon time of >90 min were randomized to facilitated PCI (with full-dose tenecteplase) or primary PCI alone. The trial was prematurely terminated by the data and safety monitoring board due to a higher 30-day mortality in the facilitated PCI arm (6.6 vs. 3.6%, $p = 0.013$). The primary end point (death, congestive heart failure, or shock at 90 days) was significantly higher in the facilitated PCI arm compared with primary PCI (18.6% vs. 13.4%, $p = 0.005$). There was also a higher rate of stroke with facilitated PCI (2.65% vs. 0.12%, $p < 0.0001$). Based on the results of this trial, one should not use thrombolytics to “facilitate” reperfusion before immediate PCI.

PCI versus thrombolysis. The optimal reperfusion strategy for elderly patients with AMI has not been well defined (6). The Senior Primary Angioplasty in Myocardial Infarction (PAMI) trial randomized 483 elderly (≥ 70 years old) patients who were thrombolytic-eligible to primary PCI versus thrombolytic with low-dose heparin (60 U/kg) (7). The trial was stopped early by the DSMB due to difficulty recruiting. The primary end point of death or disabling stroke at 30 days was 11.3% and 13.0% ($p = \text{NS}$) in the PCI and thrombolytic arms, respectively, and the secondary end point of death, reinfarction, or disabling stroke was 11.6% and 18% ($p = 0.05$). A substantial benefit was seen in patients between age 70 and 80 (37% reduction in death, 55% reduction in death, myocardial infarction, or stroke [$p < 0.001$]). However, among patients ≥ 80 years of age, the prognosis was grim in both the PCI and thrombolytic arms (death 19% vs. 16%, $p = 0.72$; death, reinfarction, or stroke, 22% vs. 22%, $p = 0.96$). This trial highlights the risk that age alone poses and demonstrates that an optimal reperfusion strategy for patients ≥ 80 years is still undefined.

Primary PCI. Few studies have evaluated whether mechanical reperfusion is beneficial in patients who present >12 h from symptom onset. The Bavarian Reperfusion Alternatives Evaluation (BRAVE)-2 investigators randomized 365 patients with STEMI (between 12 to 48 h from symptom onset) to PCI with abciximab versus conservative care (8). Infarct size measured by sestamibi was smaller in the invasive group compared with the conservative care

group (8% vs. 13%, $p < 0.001$), and there was a non-significant improvement in combined death, myocardial infarction, or stroke (4.4 vs. 6.6%, $p = 0.37$). These data suggest that asymptomatic STEMI patients may benefit from mechanical reperfusion, well beyond the traditional 12-h window.

Although stenting during primary PCI has been shown to reduce restenosis and reocclusion compared with PTCA, hard end points have not been improved. Mehta et al. (9) followed 2,087 patients who underwent primary PCI in the PAMI trials, of whom 692 received stents. Stenting resulted in better angiographic and short-term clinical outcomes, but also a sustained beneficial effect on mortality at five years.

Time-to-treatment. The National Registry of Myocardial Infarction (NRM1)-4 study has demonstrated that PCI therapy has equaled and surpassed thrombolytic therapy for treatment of STEMI in the U.S. Along with this widespread acceptance of PCI therapy, attention has turned to how to optimize results and expand availability to patients presenting to hospitals without PCI capability. Herrmann (10) nicely summarized the adverse impact of delays in transfer. In an analysis from the NRM1 3/4 registries, Nallamothu et al. (11) found that only 4% of 4,278 patients transferred for PCI were treated within 90 min of initial presentation. De Luca et al. (12) further outlined the adverse impact of time-to-treatment and found that infarct size and one-year mortality were substantially worse in patients with treatment delay. Treatment delay is not only an issue for transfer patients, but is also an important problem for off hours and weekend presentation. Magid et al. (13) reported the outcome of 33,647 patients treated with PCI from 1999 to 2002. He found that door-to-balloon times exceeding 120 min were more common during off hours. During this interval, 54% of patients were treated off hours. The median door-to-balloon time was 116 min during off hours and 94 min during working hours. In-hospital mortality was significantly higher during off hours ($p < 0.02$). These reports outline in stark detail the suboptimal system for PCI therapy that currently exists in the U.S. It is heartening to report that Bradley et al. (14) outlines concrete steps, and in particular the role of local physician champions, to improve treatment delays. These reports are a call to action in every community to improve process of care.

Table 2. Interventional Trials in Acute Myocardial Infarction in 2005

	Study Design	n	Primary Study End Point	Principal Results
Adjunctive therapies to enhance myocardial salvage				
AMISTAD-II (15)	Anterior AMI <6 h. Randomly assigned to receive a 3-h infusion of adenosine (50 or 70 $\mu\text{g/kg/min}$) or placebo.	2,118	Death, new heart failure, or first hospitalization for CHF within 6 months	No difference in clinical outcomes with adenosine. Final infarct size was smaller in the high-dose adenosine group.
CREATE-ELCA (16)	AMI <12 h Randomized to receive GIK intravenous infusion for 24 h or to usual care alone.	20,201	Mortality at 30 days	GIK infusion had no effect on mortality or any secondary outcome measures.
GIPS II (17)	AMI without signs of heart failure. Randomized to receive high-dose GIK or usual care.	731	Mortality at 30 days	No difference in mortality or enzymatic infarct size.
Ishii et al. (18)	AMI. Randomized to receive 12 mg of intravenous nicorandil or placebo just before reperfusion.	368	Cardiovascular death or admission with CHF	Lower rate of clinical events in the nicorandil arm at mean follow-up of 2.4 yrs. Improved post PCI TIMI flow 3 and STR in nicorandil group.
Adjunctive thrombectomy or embolic protection				
REMEDIA (19)	AMI <12 h. Randomized before coronary angiography to PCI with manual thrombus-aspiration or PCI alone.	100	Post-PCI TMPG ≥ 2 and STR ($\geq 70\%$)	Higher rate of post-PCI TMPG ≥ 2 and STR in manual aspiration group.
XAMINE-ST (20)	AMI <12 h. TIMI flow 0 or 1 at baseline. Randomized to stenting with or without thrombectomy using the X-Sizer device	201	STR 1 h after PCI	More complete ST-segment resolution and lower incidence of distal embolization in the X-Sizer group.
Kaltoft et al.* (21)	STEMI. Randomized to PCI plus. thrombectomy (Rescue catheter) or PCI alone.	215	Myocardial salvage at 30 days	Trend toward higher salvage in PCI alone arm. Larger final infarct size in pts treated with thrombectomy.
EMERALD (22)	AMI <6 h. Randomized to PCI with distal protection using the GuardWire device or PCI alone.	501	Infarct size by SPECT imaging 5–14 days. STR 30 min after PCI.	No difference in infarct size or ST-segment resolution with GuardWire.
PROMISE (23)	Patients with NSTEMI or STEMI <48 h. Randomized to PCI with or without distal protection using the FilterWire.	200	Maximal adenosine-induced Doppler flow velocity in the infarct related artery post PCI	No difference in Doppler flow velocity, or infarct size (MRI) with filter-based distal protection.

*Trial presented at scientific meeting but not yet published.

AMI = acute myocardial infarction; GIK = glucose-insulin-potassium infusion; PCI = percutaneous coronary intervention; MACE = major adverse cardiac events; RWM = regional wall motion; STR = ST-segment resolution.

Therapies and devices to enhance myocardial salvage. The quest to identify new pharmacologic or mechanical adjuncts to reperfusion therapy continues. Results of nine studies were reported or published in 2005 (Table 2).

The Acute Myocardial Infarction Study of Adenosine (AMISTAD)-2 trial investigated whether intravenous adenosine administered before reperfusion would reduce infarct size or improve clinical outcomes (15). Patients receiving thrombolysis or primary PCI were randomized to a 3-h infusion of adenosine (50 or 70 $\mu\text{g/kg/min}$) or placebo. There was no difference in the primary end point (new congestive heart failure, or first rehospitalization for congestive heart failure, or death within six months). However, a smaller infarct size was observed in the high-dose adenosine arm, suggesting a potential treatment effect.

Results of the Effect of Glucose-Insulin-Potassium Infusion on Mortality in Patients with Acute ST-Segment Elevation Myocardial Infarction (CREATE-ECLA) trial have now settled the question of whether glucose-insulin-

potassium (GIK) improves mortality in AMI patients (16). In this trial (the largest study of GIK therapy), 20,201 patients with STEMI presenting within 12 h from symptom onset were randomized to receive high-dose GIK infusion for 24 h or usual care. Approximately 1,800 patients in the trial were treated with primary PCI. At 30 days, there was no difference in all-cause mortality (control 9.7% vs. GIK 10.0%, $p = 0.45$), or any secondary outcome measures including cardiac arrest, cardiogenic shock, or reinfarction. Similarly, in the Glucose-Insulin-Potassium Study in Patients with ST Elevation Myocardial Infarction without Signs of Heart Failure (GIPS)-2 trial, treatment with high-dose GIK in STEMI patients without signs of heart failure did not reduce infarct size or mortality (17).

Intravenous nicorandil, a potassium channel opener and nitric oxide donor, has been shown to improve coronary artery flow and ST-segment resolution, when administered just before reperfusion. In 2005, Ishii et al. (18) reported late follow-up (mean 2.4 years) from their initial random-

ized trial and found that patients treated with nicorandil had a lower incidence of cardiovascular death or hospital admission with congestive heart failure.

The year 2005 was largely disappointing for proponents of thrombectomy or distal protection during infarct angioplasty. Two studies published this year reported positive outcomes with thrombectomy in AMI, while a third trial reported worse outcomes in thrombectomy-treated patients. In the Randomized Evaluation of the Effect of Mechanical Reduction of Distal Embolization by Thrombus-Aspiration in Primary and Rescue Angioplasty (REMEDIA) trial, use of the manual aspiration Diver catheter (Invatec S.r.l., Brescia, Italy) before stent implantation was associated with improved ST-segment resolution and myocardial perfusion (19). Similarly, in the X-SIZER in Acute Myocardial Infarction Patients for Negligible Embolization and Optimal ST Resolution (X AMINE ST) trial, adjunctive thrombectomy with the X-Sizer device (eV3, Plymouth, Minnesota) led to better ST-segment resolution (20). In contrast, Kaltoft (21) found that patients who were treated with the Boston Scientific Rescue device (Mountain View, California) had significantly larger final infarct size at 30 days compared with patients treated with PCI alone.

Continuing this theme, two studies evaluating use of distal protection devices reported negative results. In the Enhanced Myocardial Efficacy and Removal by Aspiration of Liberated Debris (EMERALD) trial, the GuardWire balloon occlusion and aspiration system (Medtronic, Santa Rosa, California) was used for embolic protection during PCI (22). Although visible debris was retrieved in 70% of cases treated with the protection device, this was not associated with any improvement in final Thrombolysis In Myocardial Infarction (TIMI) flow, myocardial perfusion, infarct size, or clinical events. In the Protection Devices in PCI-Treatment of Myocardial Infarction for Salvage of Endangered Myocardium (PROMISE) trial, a distal filter was used to limit distal embolization, but this failed to improve maximal adenosine-induced Doppler flow velocity in the infarct-related artery post-PCI or infarct size by magnetic resonance imaging (MRI) (23). Taken together, these data suggest that there is no role for routine use of thrombectomy or distal protection during mechanical reperfusion. Whether these devices are useful in patients with a large thrombus burden needs further investigation.

Cell-based cardiac repair after AMI. Use of stem cell techniques to enhance myocardial recovery after AMI was avidly investigated in 2005. The REPAIR-AMI randomized 204 AMI patients in a multicenter trial conducted in Germany and Switzerland (24). All patients underwent primary PCI with stenting followed by bone marrow aspiration four to five days later. Aspirates were sent to a central lab that processed the cells and sent back in a blinded fashion either mononuclear progenitor cells (average 236 million cells) or placebo. The infusions were given into the infarct artery through an inflated balloon catheter. At four

months, greater improvement in ejection fraction was observed in the stem cell group (5.5% vs. 3%, $p = 0.014$), and clinical events were slightly but not significantly improved. Improvement in ejection fraction was confined to subgroup with baseline ejection fraction $<49\%$, and those treated more than five days after myocardial infarction. The Effects on Left Ventricular Function by Intracoronary Injections of Autologous Mononuclear Bone Marrow Cells in Acute Anterior Wall Myocardial Infarction (ASTAMI) trial randomized 101 patients with anterior AMI treated with stenting within 12 h of symptom onset (25). Patients received either intracoronary autologous mononuclear bone marrow cells five to eight days after myocardial infarction or control. Left ventricular function was assessed at baseline and at six months by three methods: single-photon emission computed tomography, echocardiography, and MRI. There were no significant differences between the two groups in any of these measurements. In fact, MRI suggested a trend for greater improvement of ejection fraction in the control group. Another small study enrolled 35 patients with AMI treated with stenting. Although a slight improvement in ejection fraction was noted, administration of stem cells was complicated by increased coronary events (26). Among the 19 patients receiving intracoronary stem cells (CD133⁺ progenitor cells), in-stent reocclusion was noted in 2 patients, restenosis in 7 patients, and de-novo lesions in the infarct artery occurred in 2 patients. In the control group, only four cases of in-stent restenosis were observed.

It was hoped that subcutaneous injections of granulocyte colony stimulating factor (G-CSF) would be a simple noninvasive method of improving left ventricular function after AMI because it causes liberation of cells from the bone marrow thus increasing circulating stem cells. However, G-CSF also greatly increases circulating white blood cells and platelets, the effects of which in the setting of a recent AMI are unknown. The Front-Integrated Revascularization and Stem Cell Liberation in Evolving Acute Myocardial Infarction by Granulocyte Colony Stimulating Factor (FIRSTLINE-AMI) investigators reported data on 50 patients treated with G-CSF for six days versus no G-CSF after primary stenting plus abciximab (27,28). Patients treated with G-CSF had improved wall motion, left ventricular end-diastolic diameter, and ejection fraction. However, the Prospective Randomized, Double-Blind Trial of Granulocyte Colony Stimulating Factor in Patients with Acute Myocardial Infarction (REVIVAL)-2 found that G-CSF did not improve ejection fraction or infarct size measured by single-photon emission computed tomography and MRI at six months (29). In this trial, 114 AMI patients with successful PCI and baseline infarct size of at least 5% were randomized to G-CSF or placebo for five days. Although there was no improvement in infarct size or myocardial recovery, restenosis rates were not increased with G-CSF. Reports of potential complications with G-CSF have also surfaced. In one study, seven patients undergoing PCI were given G-CSF for two weeks to stimulate collateral

growth (30). Two of the seven patients developed acute coronary occlusion. A second study administered G-CSF for five days to stimulate collateral growth in 16 patients with refractory angina (31). Two of 16 patients suffered AMI, one of which was fatal. Whether these events were due to thrombocytosis, and whether more potent antiplatelet therapy would have reduced this risk is unknown.

In summary, studies published in 2005 provide conflicting, although somewhat promising, data on the role of stem cell infusion after reperfusion therapy. The exact mechanisms of action, cell type, infusion protocol, and methods of assessing efficacy remain major challenges in this field.

Cardiogenic shock. Despite advances in PCI techniques and adjunctive care, the prognosis for AMI patients who develop cardiogenic shock is dismal. Klein et al. (32) studied the outcomes of 483 shock patients in the American College of Cardiology-National Cardiovascular Data registry who underwent PCI. Although PCI was successful in 79% of patients, the in-hospital mortality was 59.4%. In addition, Klein et al. (32) developed a useful model to predict in-hospital mortality, based on four key pre-procedural variables (age, female gender, history of renal insufficiency [creatinine >2.0 mg/dl], and total occlusion of the left anterior descending coronary artery). Babaev et al. (33) reported trends in management and outcomes of shock patients among 293,633 patients in the NRM. From 1995 to 2004, there was an increase in PCI rates for shock patients from 27.4% to 54.4%. Overall in-hospital mortality for shock decreased from 60.3% to 47.9%. In a propensity-adjusted multivariable analysis, PCI was associated with improved in-hospital survival. In a report from the Should we emergently revascularize Occluded Coronaries in cardiogenic shock (SHOCK) group, White et al. (34) highlighted the importance of coronary artery bypass graft surgery (CABG) as a revascularization strategy for shock patients with extensive coronary artery disease. Finally, Dzavik et al. (35) reported on the outcomes of 56 patients age ≥ 75 years in the randomized SHOCK trial. Although patients who underwent early revascularization had a higher mortality compared with patients in the initial medical stabilization arm, there was an important imbalance in baseline characteristics in the initial medical stabilization group, including higher ejection fraction (35.6% vs. 27.5%, $p = 0.051$) and lower rate of anterior infarction (40.6% vs. 62.5%, $p = 0.11$). Based on these data, and favorable results from several other registries, PCI is reasonable to consider in selected patients 75 years or older who develop shock within 36 h of AMI.

ACUTE CORONARY SYNDROMES (ACS)

Several studies, which randomized ACS patients to early invasive versus conservative therapy, have shown clinical benefits to invasive treatment. One-year follow-up of the third Randomized Intervention Trial of unstable Angina (RITA-3) found reduced angina and improved quality of

life with invasive therapy (36). Five-year follow-up demonstrated a sustained reduction in death or myocardial infarction (odds ratio 0.78, $p = 0.044$) (37). A meta-analysis of seven trials comparing routine versus selective invasive strategies in ACS found that the invasive strategy was associated with reduced myocardial infarction, severe angina, and rehospitalization (38). Although there was a higher early mortality in the invasive arm, after discharge there were significantly fewer deaths. A larger meta-analysis of 10 trials, which randomized 9,990 patients, demonstrated a reduced rate of death or myocardial infarction with the invasive strategy (odds ratio = 0.79, $p = 0.01$) and a non-significant decrease in mortality (39). These investigators found that aggressive antiplatelet therapy ($p = 0.005$) and stenting ($p = 0.01$) were the most significant predictors of benefit.

The most recent trial randomized 1,200 patients with ACS admitted to hospitals in the Netherlands to early invasive versus selective invasive strategies (40). Although rehospitalization in the invasive group was reduced at one year (7.4% vs. 10.9%, $p = 0.04$), there was an increased risk of myocardial infarction (15.0% vs. 10.0%, $p = 0.005$), resulting in no difference in the primary end point of death, myocardial infarction, or rehospitalization. The increase in myocardial infarction observed in the trial may have been due in part to the liberal definition of periprocedural infarction.

PCI FOR CHRONIC CORONARY ARTERY DISEASE

PCI versus medical therapy or CABG. Compared with balloon angioplasty, coronary stent implantation has improved procedural success, decreased acute occlusion, need for emergency bypass, and the risk of restenosis. For these reasons, stent therapy has become the dominant method of percutaneous revascularization. Operators now routinely intervene in patient and lesion subsets that previously were the domain of cardiac surgeons. The year 2005 provided us with the first long-term results of comparative efficacy of bare-metal stents (BMS) versus coronary artery bypass surgery. Serruys et al. (41) reported the five-year follow-up of 1,205 patients with multivessel disease randomized to BMS or bypass. At five years, mortality (8% vs. 7.6%, $p = \text{NS}$) and freedom from death, stroke, and myocardial infarction (18.2% vs. 14.9%, $p = \text{NS}$) were similar for stent or bypass patients. Target vessel revascularization (TVR) was higher for the stent group (30.3% vs. 8.8%, $p < 0.001$), and a trend to higher mortality occurred in the subgroup of 208 patients with diabetes treated with stents (13.4% vs. 8.3%, $p = 0.27$). Rodriguez et al. (42) reported strikingly similar five-year results from the 450 patients treated in the Argentine Randomized Trial of Coronary Angioplasty with Stenting versus Coronary Bypass Surgery in Patients with Multivessel Disease (ERACI) II. Mortality and freedom from death/myocardial infarction were similar, but TVR was higher for the stent-treated patients.

Two large registries also reported long-term results of PCI versus CABG. Hannan et al. (43) described 37,212 patients with multivessel disease treated with bypass or stent therapy in New York State between 1997 and 2000. Malenka et al. (44) reported the outcomes in 14,493 patients with multivessel disease treated in Northern New England from 1994 to 2001. Both registries suggest a risk-adjusted survival advantage for CABG-treated patients with three-vessel disease. The New York study also suggested a three-year risk-adjusted survival advantage for patients with two-vessel disease and proximal left anterior descending coronary artery involvement who were treated with CABG. In addition, both registries report significantly higher TVR rates for stent patients. These long-term results provide fuel for controversy about the long-term impact of drug-eluting stents (DES) versus CABG in surgical candidates. This controversy will only be settled by long-term data from randomized trials that are now being conducted.

PCI for chronic total occlusion (CTO). Chronic total occlusion remains a challenge in the field of PCI. McLellan et al. (45) reviewed long-term follow-up data on 2,056 patients from the Alberta outcomes project. In this report, 648 patients had persistent total occlusions and were incompletely revascularized. At three-year follow-up, a 25% increase in the risk of death and a 45% increase in the risk of bypass occurred for patients with incomplete revascularization. Thus, methods to treat CTO continue to draw interest. Stone et al. (46,47) published two consensus papers on PCI for CTO, which nicely summarized the field. Finally, Abbas et al. (48) reported on a new technique to facilitate treatment of CTO. They describe use of an 8-h infusion of low-dose tenecteplase or alteplase in 85 patients who had previously failed standard CTO recanalization techniques and found a 54% success rate in these refractory cases. Leon et al. (49) took a different approach by randomizing patients with incomplete revascularization to direct laser transmyocardial laser revascularization TMR versus sham therapy in the Direct myocardial revascularization In Regeneration of Endomyocardial Channels (DIRECT) trial. Patients were randomized to low-dose, high-dose myocardial laser channels, or sham. Laser-treated patients had a higher rate of 30-day myocardial infarction and no improvement in anginal status or exercise duration compared to control.

Factors influencing clinical outcomes after elective PCI. The most modifiable risk factor for complications and mortality after PCI is the skill and experience of the operative team. Hannan et al. (50) report that in the New York State database of 107,713 PCIs performed between 1998 to 2000 that low-volume operators (<75 cases/year) working in low-volume hospitals (<400 cases/year) had a six-fold increase in the risk of same-day bypass and a four-fold increase in the risk of death compared with high-volume operators and hospitals. Similarly, Moscucci et al. (51) examined the Michigan Blue Cross consortium

outcome data and found that MACE events were significantly higher for operators doing <89 cases per year ($p < 0.0001$). These two studies provide strong incentives to limit the unbridled expansion of PCI facilities.

Cram et al. (52) studied whether opening of cardiac surgical hospitals might improve outcomes. They report on the Medicare database during 2000 and 2001 when 69,000 patients had PCI or CABG in 15 specialty hospitals. Outcomes were compared with patients treated in general hospitals. Volumes were greater for both PCI and CABG in the specialty hospitals, and unadjusted 30-day mortality was lower. The mortality differences largely disappeared after risk adjustment. They concluded that specialty hospitals have improved outcomes due to case selection and higher procedural volumes.

Moscucci et al. (53) further provide provocative data suggesting that high-risk patients may be orphaned by public reporting. They reviewed the outcome experience in New York State where public reporting is state mandated and in Michigan where it is not, for the years 1998 and 1999. Crude unadjusted mortality was higher in Michigan (1.54% vs. 0.83%, $p < 0.0001$). After adjusting for comorbidities, no difference in mortality existed. More patients with cardiogenic shock (14.4% vs. 8.7%, $p < 0.001$), congestive heart failure, and extracardiac vascular disease were treated in Michigan. The authors conclude that public reporting in New York may cause patient selection bias that precludes treatment of high-risk patients.

Further data is accumulating on the adverse risk that chronic kidney disease (CKD) poses for PCI patients. Ix et al. (54) describe 290 patients who had CKD and were treated with PCI ($n = 151$) or bypass ($n = 139$) in the Arterial Revascularization Therapies Study (ARTS)-I. Major adverse cardiac events were significantly greater for both PCI and CABG patients when CKD was present. Similarly, Lemos et al. (55) reported that mortality at one year was greater (7.6% vs. 2.5%) for patients with CKD with no difference whether or not DES were employed. Target vessel revascularization was reduced by DES implantation (relative risk = 0.37, confidence interval = 0.15 to 0.90, $p = 0.03$). Finally, Dangas et al. (56) reported that contrast-induced nephropathy dramatically escalates one-year mortality in PCI patients with CKD. Importantly, a 75% one-year mortality occurred for patients with CKD that required new dialysis because of contrast-induced nephropathy. These trials all continue to draw attention to this high-risk population and this potentially lethal complication of PCI.

Cell and subcellular therapies for chronic ischemia. Although intracoronary infusion of stem cells may be beneficial after recent AMI, patients with remote infarction or chronic angina no longer release chemotactic factors allowing homing of stem cells to the affected area. Therefore, most studies have utilized needle injections of stem cells for chronic angina or heart failure. The Direct Intramyocardial Plasmid Vascular Endothelial Growth

Factor-A₁₆₅ Gene Therapy in Patients with Stable Severe Angina Pectoris (EUROINJECT-One) trial was a double blind, randomized trial of 80 patients with class 3 to 4 angina who received either intramyocardial injections of plasmid vascular endothelial growth factor A or placebo (57). Procedure-related adverse events occurred in 5 of 40 patients (12.5%) randomized to plasmid vascular endothelial growth factor A. At three months, there was no difference in stress myocardial perfusion defects between the two groups. Interestingly, vascular endothelial growth factor gene transfer improved regional wall motion and angina class, suggesting a favorable anti-ischemic effect even though the primary end point was negative. Strauer et al. (58) reported results in 18 patients with remote myocardial infarction (five months to eight years earlier) in whom bone marrow cells were infused through an inflated balloon catheter in the coronary artery. At three months, infarct size was reduced by 30%, ejection fraction improved by 15%, no arrhythmias were observed, and only one patient developed restenosis.

New technologies to affect endothelial healing are being investigated. The Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth (HEALING) registry treated 16 patients with de-novo coronary disease with a stainless steel stent coated with murine monoclonal CD-34 antibodies (59). This stent captures endothelial progenitor cells with in-vivo studies showing >90% coverage at 1 h, allowing inhibition of thrombus formation and reduced neointimal proliferation. In this 16-patient registry, no patient experienced subacute thrombosis despite discontinuation of clopidogrel at day 28. At six-month angiography, restenosis occurred in two patients (13%), and late loss was 0.63 ± 0.52 mm. The HEALING II registry will test newer stent technology with greater preservation of antibody structure and bioactivity.

The PROject of Ex-vivo Vein Graft ENgineering via Transfection (PREVENT)-4 study randomized 3,014 patients undergoing CABG with at least two saphenous vein grafts (SVG) to receive SVGs pretreated with placebo or edifoligide (transcription factor inhibitor intended to suppress neointimal hyperplasia) (60). The primary end point of death or SVG failure (stenosis >75%) in at least one SVG by angiography at 18 months was not reduced by transcription factor inhibition, whether measured per patient (45.2% vs. 46.3%, $p = 0.66$) or per SVG (28.5% vs. 29.7%, $p = 0.44$).

THERAPIES FOR THE PREVENTION OF RESTENOSIS

DES. COMPARATIVE TRIALS OF SIROLIMUS-ELUTING STENTS (SES) VERSUS PACLITAXEL-ELUTING STENTS (PES). In the year 2004, we witnessed the widespread adoption of DES after approval of the Cypher (Johnson & Johnson) and Taxus (Boston Scientific) systems in the U.S. Detailed comparison of the two systems occurred in 2005. Kastrati et al. (61) summarized the completed comparison trials. Kastrati et al. (62) also reported the Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for In-Stent Restenosis (ISAR-DESIRE) trial in which 300 patients with in-stent stenosis were randomized to treatment with brachytherapy ($n = 100$), paclitaxel ($n = 100$), or sirolimus ($n = 100$). Dibra et al. (63) studied 250 patients with diabetes who were randomized to paclitaxel ($n = 125$) or sirolimus ($n = 125$) in the Intracoronary Stenting and Angiographic Results: Do Diabetic Patients Derive Similar Benefit from Paclitaxel-Eluting and Sirolimus-Eluting Stents (ISAR-DIABETES) trial. Goy et al. (64) studied the seven-month clinical outcome of 202 patients treated with paclitaxel or sirolimus. In contrast with these small trials, three large randomized trials were reported in 2005 including Sirolimus-Eluting and Paclitaxel-Eluting Stents

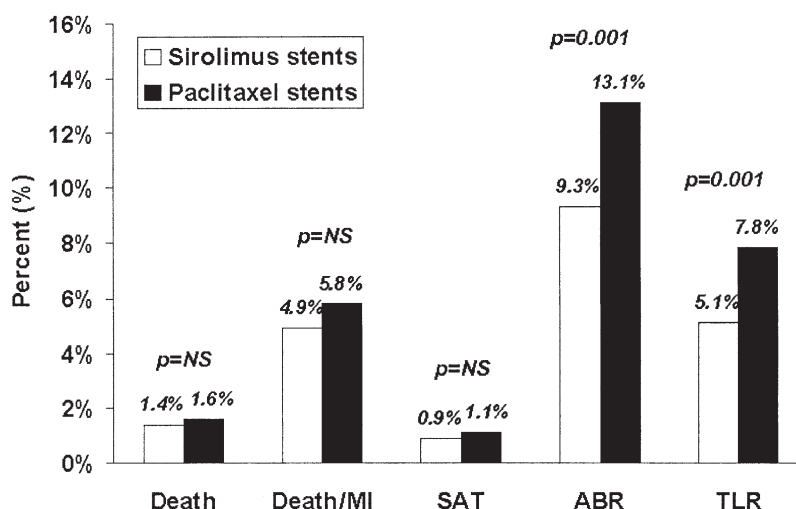


Figure 1. Clinical outcome in patients treated with a sirolimus-eluting or paclitaxel-eluting stent. Data are summarized from the Kastrati et al. (61) meta-analysis of published randomized trials of paclitaxel vs. sirolimus stents. ABR = angiographic binary stenosis; MI = myocardial infarction; SAT = subacute thrombosis; TLR = target lesion revascularization.

for Coronary Revascularization (SIRTAX) (65), Prospective Randomized Multi-Center Head-to-Head Comparison of the Sirolimus-Eluting Stent (Cypher) and the Paclitaxel-Eluting Stent (Taxus) (REALITY) (66), and Drug-Eluting Stents for Complex Lesions: Randomized Rapamycin Versus Paclitaxel (CORPAL) (67). These trials randomized 1,012, 1,353, and 652 to SES or PES. Of these trials, only the SIRTAX trial has been published (65). In the Kastrati et al. (61) meta-analysis, all six trials were pooled to describe angiographic and clinical outcome for 3,669 patients (Fig. 1). At follow-up, mortality was 25 of 1,845 for the SES group versus 29 of 1,824 in the PES group ($p = \text{NS}$). Death or myocardial infarction occurred in 91 of 1,845 and 106 of 1,824 for sirolimus- or paclitaxel-treated patients, respectively ($p = \text{NS}$). Stent thrombosis was infrequent and similar for both groups (17 of 1,845 vs. 20 of 1,824, $p = \text{NS}$). Although major safety measures were similar, angiographic results favored sirolimus; target lesion revascularization (TLR) was 5.1% vs. 7.8% ($p = 0.001$), and angiographic restenosis was 9.3% versus 13.1% ($p = 0.001$). Two other reports also demonstrated that the initial benefit of SES is maintained at late follow-up (68,69). Because major safety data were similar and TLR was low for both groups, it is likely that other factors such as stent availability, deliverability, and cost will play a larger role in stent selection in the U.S. in 2006.

NON-FDA-APPROVED DES. The Randomized Comparison of the Endeavor ABT-578 Drug Eluting Stent With a Bare Metal Stent for Coronary Revascularization (ENDEAVOR) II trial was a multicenter, international trial randomizing 1,195 patients with de-novo coronary lesions to receive the Medtronic ABT-578 (a rapamycin analogue) Endeavor stent versus the Medtronic Driver cobalt alloy stent (70). The primary end point of target vessel failure at nine months (TVR, myocardial infarction, or cardiac death) was reduced in the DES group (8.1% vs. 15.4%, $p < 0.0005$), primarily due to reduced TVR. Although restenosis rates (9.5% vs. 32.7%, $p < 0.0001$) and late loss (0.62 mm vs. 1.03 mm) were reduced with the Endeavor stent, it was not as low as that observed with FDA-approved DES.

The Randomized Comparison of Zotarolimus-Eluting and Sirolimus-Eluting Stents in Patients With Coronary Artery Disease (ENDEAVOR)-III trial randomized 436 patients to receive the Endeavor DES versus the Cypher SES (71). Although MACE was similar, TLR tended to be higher with the Endeavor stent (6.3% vs. 3.5%), and in-segment late loss was significantly greater (0.34 mm vs. 0.13 mm, $p < 0.001$), as was in-stent late loss (0.60 mm vs. 0.15 mm, $p < 0.001$) and in-stent restenosis (9.2% vs. 4.3%, $p = 0.04$). Medtronic has embarked on another trial, which will randomize 1,548 patients to Endeavor versus the Taxus PES.

The Yukon Nonpolymer-Based Rapamycin-Coated Stent and the Polymer-Based Paclitaxel-Eluting Stent in Patients With Coronary Artery Disease (ISAR-TEST) trial ran-

domized 450 patients to receive the Yukon DES (Transluminia, Hechingen, Germany), which has a microporous surface coated with rapamycin (polymer-free) compared with the polymer-based paclitaxel stent (72). At nine-month follow-up, clinical outcomes were similar. Angiographic restenosis was 14.2% versus 15.5% ($p = 0.73$), in-stent late loss 0.48 mm versus 0.48 mm, and in-segment late loss was 0.34 mm versus 0.24 mm ($p = 0.09$) in the non-polymer- and polymer-based stents, respectively. The investigators concluded that the antirestenotic effect of the Yukon DES was not inferior to that of the Taxus polymer-based DES.

The Tacrolimus-Eluting Stent Compared to a Carbon-Coated Stent in Patients With Coronary Artery Disease (JUPITER) II trial randomized 332 patients to receive the polymer-free Janus Tacrolimus-eluting Carbo stent (Sorin Biomedica Cardio, Saluggia, Italy) (drug reservoirs on outer surface of stent) versus the Tecnic Carbostent (Sorin Biomedica Cardio) (73). Although there was a trend for reduction in TLR and restenosis in the Janus group, angiographic follow-up at six months demonstrated no difference in late loss. Whether this disappointing result was due to a better than expected outcome in the bare stent versus the drug or eluting kinetics is unknown.

A small study randomized 42 patients to receive an everolimus-eluting stent ($n = 27$) versus a BMS ($n = 15$) (74). At six-month angiographic follow-up, everolimus significantly reduced late loss (0.10 mm vs. 0.85 mm, $p < 0.0001$), and there was no stent thrombosis or aneurysm formation. The late loss of 0.1 mm is similar to sirolimus; both drugs have the same pathway to inhibit smooth muscle cell proliferation.

By the end of 2005, 27 randomized trials have been conducted comparing BMS to DES. The impact of angiographic late loss is summarized in Figure 2. In aggregate, these trials suggest that an efficacy boundary of a late loss of 0.6 mm exists. Because randomization to BMS is unlikely in the future, it is likely that an efficacy target of angiographic late loss will become a performance standard (75).

STENT THROMBOSIS WITH DES. A series of articles in 2005 addressed the safety of DES. Hwang et al. (76) suggested that intraluminal clot decreases paclitaxel absorption in a rat model. Whether this translates to decreased efficacy or worse safety in patients with AMI is currently being tested in the Harmonizing Outcomes with Revascularization and Stents (HORIZONS) trial. A concern has been voiced regarding the incidence of subacute thrombosis in patients treated with DES. To address this issue, Bavry et al. (77) pooled data from eight randomized trials of PES versus placebo, while Moreno et al. (78) pooled data from 10 randomized trials of SES and PES. Both studies found that subacute thrombosis was low and similar for DES and BMS systems.

One mechanism for late stent thrombosis may be initial or acquired malapposition of DES. Fujii et al. (79) reviewed

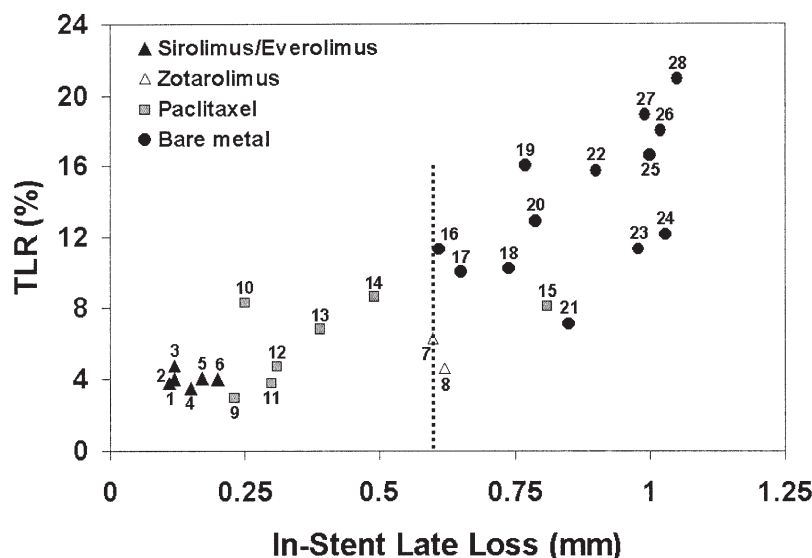


Figure 2. Relationship between late loss and target lesion revascularization (TLR) in clinical trials evaluating bare metal and drug-eluting stent platforms. **Solid triangles** = sirolimus-, everolimus-eluting stent; **open triangles** = zotarolimus-eluting stent; **solid squares** = paclitaxel-drug-eluting stent; **solid circles** = bare metal stent. Target lesion revascularization is at nine months unless indicated. *Target lesion revascularization at 6 months; †target lesion revascularization at 12 months. 1 = FUTURE-I*; 2 = C-SIRIUS; 3 = SIRTAX; 4 = ENDEAVOR-III; 5 = SIRIUS; 6 = E-SIRIUS; 7 = ENDEAVOR-III; 8 = ENDEAVOR-II; 9 = TAXUS-IV; 10 = SIRTAX; 11 = TAXUS-II (slow release group)†; 12 = TAXUS-II (moderate release group)†; 13 = TAXUS-VI; 14 = TAXUS-V; 15 = DELIVER; 16 = TAXUS-IV; 17 = BENESTENT (stent group); 18 = STRESS (stent group); 19 = TAXUS-II (moderate release group)†; 20 = TAXUS-II (slow release group)†; 21 = FUTURE-I; 22 = TAXUS-V; 23 = DELIVER; 24 = ENDEAVOR-II; 25 = SIRIUS; 26 = C-SIRIUS; 27 = TAXUS-VI; 28 = E-SIRIUS. Abbreviations as in Table 1.

intravascular ultrasound data on 15 patients with subacute thrombosis after Cypher stent implantation. Rather than stent malapposition, stent under expansion was present in most cases of subacute thrombosis. Tanabe et al. (80) reported intravascular ultrasound findings in the Taxus II trial. Late stent malapposition occurred in 5.4% of BMS and 8.7% of paclitaxel stents ($p = \text{NS}$). Late malapposition was not associated with subacute thrombosis. Intravascular ultrasound follow-up in the Sirolimus-coated Bx Velocity Balloon-Expandable Stent (SIRIUS) trial demonstrated a higher rate of late acquired malapposition in Cypher-treated patients (0% vs. 8.7%, $p < 0.05$), but as in the TAXUS II trial, no adverse clinical events occurred with late stent malapposition (81). For this reason, other mechanisms for late subacute thrombosis have been studied. Ong et al. (82,83) reported that termination of dual antiplatelet therapy exacerbates risk of subacute thrombosis, as long as 14.5 months after stent implantation. Therefore, long-term dual antiplatelet therapy may be required in some patients, especially in anatomic subsets like left main coronary artery stenting when subacute thrombosis could be lethal.

NEW LESION SUBSETS. The pivotal randomized trials that led to approval of the Cypher and Taxus stents included only short, simple coronary lesions. The cost effectiveness of DES in simple lesions was questioned in the Basel Stent Kosten Effektivitats Trial (BASKET) (84). In this study, 736 patients were randomized to SES, PES, or cobalt-chromium stents. Although the combined end point of death/myocardial infarction/TVR was lower at one year for the DES patients (7.2% vs. 12.1%, $p = 0.02$), the one-year

costs were significantly higher for the DES-treated patients. Because TVR rates were so low, the added costs of treating all low-risk patients was not overcome by less restenosis interventions at one year.

The year 2005 brought more data on complex lesion subsets that were not previously reported. In this regard, the TAXUS V trial reported by Stone et al. (85) and the TAXUS VI trial reported by Dawkins et al. (86) add new information. Both trials randomized patients with long, complex coronary lesions. Stone et al. (85) reported a reduction of nine-month TLR from 15.7% to 8.6% ($p < 0.001$), and Dawkins et al. (86) reported a decrease in TLR from 18.9% to 6.8% ($p = 0.0001$). No safety concerns were reported. Similarly, the Stenting of Coronary Arteries in Non-Stress/Benestent Disease (SCANDSTENT) trial demonstrated a significant reduction in TLR and MACE among patients with complex coronary lesions who received an SES compared with a BMS (87).

Sabaté et al. (88) randomized 160 patients with diabetes to treatment with BMS or SES. He found that angiographic late lumen loss was significantly reduced by the Cypher stent (0.47 ± 0.5 mm vs. 0.06 ± 0.4 mm, $p < 0.001$). There was no difference in efficacy for oral hypoglycemic therapy or insulin-treated patients. Hermiller et al. (89) presented results of the PES in patients with diabetes randomized in the TAXUS IV trial. Among the 318 patients (108 insulin dependent) studied, angiographic binary restenosis was reduced by 81% in PES-treated patients (34.5% vs. 6.4%, $p < 0.0001$). Thus, both PES and SES systems appear especially useful in patients with diabetes.

These data are particularly important in light of the powerful impact that diabetes has on restenosis. Among 11,484 patients enrolled in the Prevention of Restenosis with Tranilast and its Outcomes (PRESTO) trial, Singh et al. (90) found that diabetes, long lesions, ostial lesions, and left anterior descending coronary artery location significantly increased the risk for TVR in patients treated with BMS.

Because left anterior descending coronary artery lesion location predisposes to restenosis, the efficacy of DES in this location is of particular interest. Dangas et al. (91) reported on the 536 patients in TAXUS IV who were randomized to BMS or PES. Binary restenosis was reduced from 26.9% to 11.3% ($p = 0.004$), and one-year MACE events were decreased from 21.2% to 13.5% ($p = 0.01$). Seung et al. (92) studied use of the SES in the ostial left anterior descending coronary artery location. In this consecutive series, 68 patients with SES were compared with 77 patients treated with BMS before the two years prior to SES availability. Angiographic restenosis was lower with in the SES group (5.1% vs. 32.3%, $p < 0.001$). Importantly, no left main restenosis occurred with SES, whereas 7% of BMS-treated patients had left main restenosis. Finally, Tsagalou et al. (93) reported on the 66 patients with left anterior descending coronary artery-treated location that had >60 mm of stent length. They found a high incidence of periprocedural myocardial infarction (17%), and a 15% rate of TVR occurred. Thus, it appears that significant progress has been made in treatment of left anterior descending coronary artery disease, but obstacles including major side branch compromise and periprocedural myocardial infarction still need to be overcome.

With the decline in the risk of restenosis, enormous enthusiasm has risen for use of DES in patients with left main disease. Park et al. (94) reported on 102 patients treated with SES from March 2003 to March 2004 and compared outcomes to historical controls treated with BMS. Their technical approach has changed in the DES era. More stents are used, more bifurcation disease is treated, and less atherectomy debulking occurs. Importantly, angiographic restenosis is lower (7.0% vs. 30.3%, $p < 0.001$), and freedom from MACE is higher (98% vs. 81%, $p = 0.0003$) for patients treated with SES. The Thorax-center group reported similar results (95). Target vessel revascularization rates were lower (6% vs. 23%, $p = 0.004$) in the 95 patients treated with DES compared with a historical control group of 86 patients treated with BMS. Similarly, Chieffo et al. (96) found a lower rate of MACE at six months in 85 patients who were treated with a DES compared with historical controls (20% vs. 35.5%, $p = 0.039$). These three studies add great impetus for the conduct of randomized trials of PCI with DES versus CABG in this high-risk patient population.

In 2005, Valgimigli et al. (97) reported results of the first randomized trial of DES in patients with AMI. A total of 175 patients were randomized to receive an SES plus

tirofiban or BMS plus abciximab. The primary study end point, a composite of death, non-fatal myocardial infarction, stroke, or binary restenosis, was significantly lower in the DES group (19% vs. 50%, $p < 0.001$), driven mainly by a lower rate of binary restenosis in the DES group (9% vs. 36%, $p = 0.002$). There was no difference in the incidence of stent thrombosis. Although these data are promising, larger studies are needed before routine use of DES for patients with AMI can be recommended.

Additional lesion subsets that have shown good clinical outcomes and low restenosis rates in studies include SVGs (98), ACS (99), in-stent restenosis (100), and CTO (101,102).

DES VERSUS BRACHYTHERAPY. Until recently, vascular brachytherapy was the only effective treatment for patients with bare metal in-stent restenosis. The Sirolimus-Eluting Stent Versus Brachytherapy in Patients With Bare Metal In-Stent Restenosis (SISR) trial, designed to compare the efficacy of an SES versus brachytherapy, enrolled 384 patients with in-stent restenosis in native coronary arteries (103). Target vessel failure, the primary end point, was significantly reduced in the SES group compared with brachytherapy (12.4% vs. 21.6%, $p = 0.023$). Angiographic analysis demonstrated greater distal edge late loss in the brachytherapy group. Overall, these results indicate that use of SES is superior to brachytherapy for the prevention of recurrent in-stent restenosis.

New non-drug-coated stents. A novel strategy to limit stent restenosis is the use of a titanium-nitride-oxide stent coating. This material, which has a superior biocompatibility to stainless steel, has been shown in vitro to reduce vascular inflammation and neointimal hyperplasia. In a randomized trial reported this year, Windecker et al. (104) found that patients treated with a titanium-nitride-oxide stent had a significantly lower late loss (0.55 mm vs. 0.90 mm, $p = 0.03$), binary restenosis (15% vs. 33%, $p = 0.07$), and neointimal volume (18 vs. 48 mm³, $p < 0.0001$) compared with patients who received a non-coated stent.

Adjunctive pharmacologic therapy to limit restenosis. Oral medications to reduce restenosis may be of benefit. Cilostazol (Otsuka American Pharmaceuticals, Rockville, Maryland), a platelet-aggregation inhibitor, appears to be a beneficial adjunct for patients who are treated with a BMS during coronary revascularization. In the multicenter Cilostazol for Restenosis Trial (CREST), patients assigned to cilostazol therapy had a significant reduction in angiographic restenosis at six months (105). Importantly, a benefit was also seen in subjects with diabetes and small vessels.

Pioglitazone (Takeda Pharmaceuticals, Osaka, Japan), an oral diabetic agent, also appears to have antirestenotic properties. Marx et al. (106) randomized 50 patients without diabetes undergoing stent implantation to pioglitazone (30 mg/day) or placebo for six months. At six-month follow-up, patients treated with pioglitazone had a signifi-

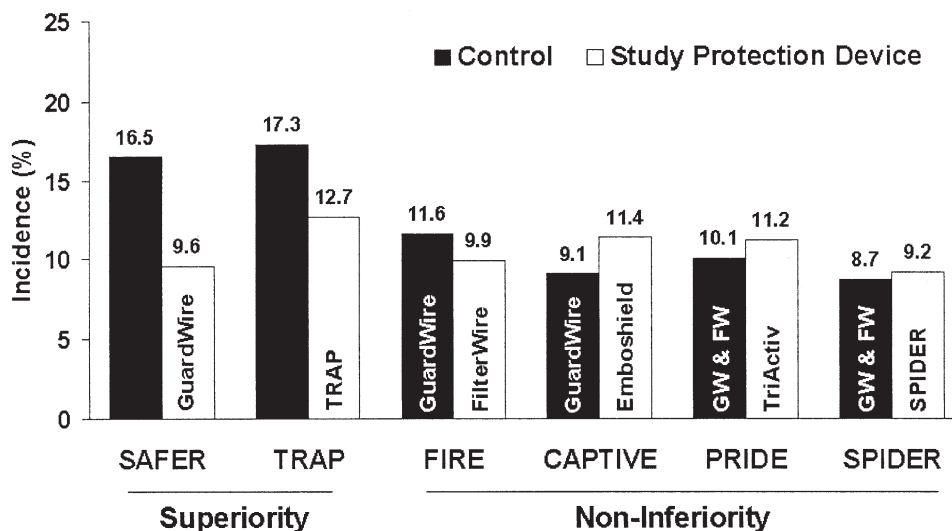


Figure 3. Incidence of major adverse cardiac events at 30 days in six trials evaluating embolic protection devices during saphenous vein graft intervention. FW = FilterWire; GW = GuardWire.

cantly reduced neointimal volume within the stented segment and lower binary restenosis rate compared with control patients (3.4% vs. 32.3%, $p < 0.01$).

Zohnhofer et al. (107) studied the use of systemic imatinib, a potent platelet-derived growth factor receptor kinase inhibitor, for the prevention of recurrent restenosis in 180 patients with in-stent restenosis. Angiographic follow-up, however, demonstrated no difference in the rate of recurrent restenosis.

EMBOLIC PROTECTION DEVICES

The SPIDER trial evaluated a novel nitinol mesh filter during SVG intervention (108). One of the major advantages of this filter is that the operator may cross the lesion with a conventional guidewire before deploying the protection device. The trial randomized 732 patients to undergo PCI with either the SPIDER (eV3, Plymouth, Minnesota) device or an approved control device (Fig. 3). At 30 days, the primary study end point MACE occurred in 9.2% of patients in the SPIDER arm and 8.7% of patients in the control arm ($p = 0.012$ for non-inferiority). The Protection During Saphenous Vein Graft Intervention to Prevent Distal Embolization (PRIDE) trial compared the efficacy of the TriActiv distal balloon occlusion system (Kensey Nash, Exton, Pennsylvania) with either the GuardWire (Medtronic) or FilterWire EX (Boston Scientific) devices (109). After PCI, there was no significant difference in the incidence of final TIMI flow grade 3 between the study groups (TriActiv 99.1% vs. control group 97.8%, $p = 0.20$). At 30 days, the primary end point (MACE) was similar in the TriActiv and control groups. These data suggest that both the SPIDER and TriActiv devices provide an equivalent degree of embolic protection to currently available distal protection systems.

Another method of limiting embolization during SVG intervention is to employ a proximal protection device. The

Proximal Protection During Saphenous Vein Graft Intervention Using the Proxis Embolic Protection System (PROXIMAL) trial was a non-inferiority trial, comparing the Proxis system (St. Jude Medical, St. Paul, Minnesota) to protection with either the FilterWire or GuardWire distal protection devices (110). The 30-day MACE rate was 9.2% in the Proxis arm and 10.0% in the control arm, suggesting that the proximal protection system provided equivalent protection to the distal devices. This system may be particularly useful for patients in whom graft anatomy is not suitable for use of a distal protection system.

Since the introduction of embolic protection systems, there has been debate about the relative benefits of occlusive versus filter-based devices. Rogers et al. (111) performed a morphometric analysis of particulate debris liberated during SVG intervention and found that the volume of embolic material was equivalent between filter devices and distal or proximal balloon occlusion devices. Finally, in a report from the Saphenous vein graft Angioplasty Free of Emboli Randomized (SAFER) trial, Giugliano et al. (112) demonstrated that the risk of distal embolization is independently associated with more diffuse graft disease and bulkier lesions. However, the GuardWire device was also found to be beneficial in patients with less extensive disease, suggesting that embolic protection should be employed on a routine basis during SVG intervention.

AORTIC AND CAROTID ARTERY DISEASE

This year further data emerged on the treatment of carotid and aortic disease. Long-term follow-up is now available concerning percutaneous repair of abdominal aortic aneurysm. Initial reports describing early (30-day) outcome suggested that the percutaneous approach had a safety advantage over open repair. In 2005, the Dutch Randomized Endovascular Aneurysm Management (DREAM) study from the Netherlands (113) and the Endovascular

Aneurysm Repair (EVAR) 1 study from Britain (114) provided long-term efficacy data. In the DREAM trial, 351 patients with abdominal aortic aneurysm >5 cm were randomized and had two-year survival reported. Although the stent group had an early survival advantage, at two years, Kaplan-Meier survival probability was 89.6% versus 89.7%, and survival free of serious complications was 65.9% versus 65.6% ($p = \text{NS}$) for surgery versus stent therapy. Similarly, the EVAR 1 investigators randomized 1,082 patients to open repair ($n = 543$) or stent ($n = 539$) therapy. At four years, mortality was 28% for both groups. Importantly, postoperative complications were 41% versus 9% for the stent versus open repair ($p < 0.001$), and costs were higher for stent therapy. These two trials suggest that, in good surgical candidates, no long-term survival advantage occurs for stent graft therapy. Furthermore, stent graft therapy requires detailed surveillance because a high percentage of these patients develop postoperative complications. Finally, the EVAR investigators also reported a randomized trial in 338 patients with abdominal aortic aneurysm that were not surgical candidates (115). As expected, survival with medical therapy was 64% in four years. Unfortunately, stent therapy did not improve survival. In summary, as of 2005, stent graft therapy offers no long-term survival advantage over open surgical repair of abdominal aortic aneurysm and is associated with higher follow-up costs and complications. In poor surgical candidates, this therapy still remains unproven.

In 2005, Rosenfield et al. (116) published a consensus document on training and competence for performance of carotid stenting. Casserly et al. (117) described the impact of slow flow after carotid stenting. Slow angiographic flow occurred in 10% of 414 patients treated with carotid stenting and distal protection devices. This had adverse consequences because post-operative stroke occurred in 9.5% versus 1.7% ($p = 0.03$) of these patients.

ADJUNCTIVE PHARMACOLOGY

Antiplatelet therapy. STEMI/ACS. A meta-analysis of all randomized trials of abciximab in AMI (involving 27,115 patients) found that abciximab reduced 30-day reinfarction overall (2.1% vs. 3.3%, $p < 0.001$), as well as in subgroups treated with thrombolysis or with primary angioplasty (118). In the primary PCI group, abciximab treatment was associated with reduced mortality at 30 days (2.4% vs. 3.4%, $p = 0.047$) and long-term (6 to 12 months) (4.4% vs. 6.2%, $p = 0.01$) with no increased risk of major bleeding. Conversely, in thrombolytic-treated patients, abciximab did not reduce mortality but significantly increased the risk of major bleeding (5.2% vs. 3.1%, $p < 0.001$).

ELECTIVE PCI. Although abciximab is beneficial in patients undergoing PCI for ACS or STEMI, it is not known whether a 12-h infusion is necessary in elective PCI patients, or whether a single bolus is adequate. The Same-Day Home Discharge After Transradial Coronary Stenting

With a Single Abciximab Bolus (EASY) trial randomized 1,005 patients who underwent transradial stent implantation with abciximab bolus, to receive either a 12-h abciximab infusion and overnight hospitalization versus bolus only and discharge 4 to 6 h after PCI (119). Clinical outcomes at 30 days and 6 months were similar between the two groups, and 88% of the bolus-only group was safely discharged the same day.

Some patients with definite indications for aspirin and clopidogrel have a history of allergy to aspirin. Silberman et al. (120) reported 16 patients with ACS who underwent rapid aspirin desensitization. Beta-blockers were withheld, and patients were monitored in the coronary care unit with peak expiratory flow measured every 30 min along with vital signs and visual allergy assessments. Patients underwent rapid desensitization over 2.5 to 3.5 h starting with low doses of aspirin (1 to 5 mg), with doubling of the dose every 30 min until 80 to 100 mg was given. Successful tolerance was induced in 93.5% of patients, allowing PCI and long-term use of aspirin.

Clopidogrel “resistance” has been described in several reports. Serebruany et al. (121) suggested that clopidogrel response is not dichotomous, but followed a normal bell-shaped distribution in a study of 544 patients. The mean response was $41.9 \pm 20.8\%$ when platelet aggregation was induced by $5 \mu\text{mol/l}$ of adenosine diphosphate. Hyporesponsiveness, defined as two standard deviations less than the mean, occurred in 4.2% of patients.

The clinical implications of clopidogrel “hyporesponsiveness” were described in two reports. Gurbel et al. (122) performed platelet studies in 20 patients with subacute stent thrombosis and compared them with 100 age-matched control patients without stent thrombosis. Subacute thrombosis patients had incomplete P2Y₁₂ receptor inhibition and greater platelet aggregation to $5 \mu\text{mol/l}$ adenosine diphosphate ($49 \pm 4\%$ vs. $33 \pm 2\%$, $p < 0.05$). In another study of 192 patients, platelet reactivity to adenosine diphosphate was predictive of ischemic events post-PCI, but clot strength (a measure of thrombin-induced fibrin and platelet interactions measured by thromboelastography) was the best predictor of ischemic events (123).

What can be done to reduce platelet hyporesponsiveness? In a randomized study of 190 patients, the incidence of non-responsiveness (defined as $<10\%$ absolute change in platelet aggregation) was reduced from 28% with 300-mg loading dose of clopidogrel to 8% with a 600-mg dose (124). Another randomized study of 60 patients confirmed that a 600-mg loading dose of clopidogrel resulted in higher plasma concentrations of the active metabolite and less platelet aggregation at 4 h compared with the 300-mg loading dose (125). However, there was no additional benefit to the 900-mg loading dose, suggesting limited clopidogrel absorption. Hochholzer et al. (126) performed platelet aggregation studies in 1,001 patients before 600 mg clopidogrel and at the time of catheterization (performed at variable time intervals). The full antiplatelet effect of 600

mg clopidogrel (assessed by platelet aggregation, surface expression of P-selectin, and activated glycoprotein IIb/IIIa) was achieved after 2 h. These data suggest that 600 mg clopidogrel should be given instead of 300 mg, and administered at least 2 h before PCI.

The clinical relevance of different loading doses of clopidogrel was assessed in the Antiplatelet Therapy for Reduction of Myocardial Damage during Angioplasty (ARMYDA)-2 study (127). These investigators randomized 255 patients undergoing PCI to 600 mg versus 300 mg clopidogrel, given 4 to 8 h before PCI. Periprocedural myocardial infarction was significantly lower in the group that received the 600-mg clopidogrel loading dose.

As expected, the addition of a glycoprotein IIb/IIIa agent provides greater platelet inhibition, compared with either 300 mg or 600 mg clopidogrel (128). Whether this will translate to improved clinical outcomes has yet to be tested. There is, however, evidence that triple versus dual antiplatelet therapy is of clinical benefit. Lee et al. (129) reported an observational study of 3,012 stent patients, all of whom received at least dual antiplatelet therapy with aspirin and adenosine diphosphate antagonist (clopidogrel or ticlopidine, given more than two days in advance in 84% of patients). Approximately half of the group received double ($n = 1,597$) and the remainder triple antiplatelet therapy ($n = 1,415$) (with an additional cilostazol 200-mg load followed by 100 mg twice a day). No DES or glycoprotein IIb/IIIa antagonists were utilized. Despite more multivessel stenting and use of long stents in the triple antiplatelet group, stent thrombosis within one month was lower (0.1% vs. 0.5%, $p = 0.024$). Predictors of stent thrombosis included primary stenting for AMI and not using cilostazol. Triple antiplatelet therapy was well tolerated with the exception of a slight increase in skin rashes (1.1% vs. 0.5%, $p = 0.079$). Given this observational report, as well as the prospective, randomized CREST trial, consideration should be given to adding cilostazol to patients at high risk of stent thrombosis or restenosis.

Finally, the Joint Utilization of Medications to Block Platelets Optimally-Thrombolysis In Myocardial Infarction 26 (JUMBO-TIMI 26) trial evaluated the use of prasugrel,

a novel thienopyridine P2Y₁₂ receptor antagonist, in 904 patients undergoing elective or urgent PCI (130). Prasugrel was found to be safe with no increased risk of bleeding complications compared with clopidogrel, and there was a lower incidence of 30-day MACE in the prasugrel group.

Antithrombin therapy. Because of the limitations of unfractionated heparin, several alternative antithrombotic agents have been evaluated to improve the outcomes of PCI. The Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIB/IIA Inhibitors (SYNERGY) trial compared enoxaparin and unfractionated heparin in high-risk patients with ACS who were expected to undergo early invasive therapy. At 30 days, enoxaparin was found to be non-inferior to unfractionated heparin in reducing death or non-fatal reinfarction. In 2005, the six-month and one-year outcomes of the SYNERGY trial were reported (131). At follow-up, there was a fairly high rate of recurrent cardiac events; however, patients receiving enoxaparin had similar rates of death or myocardial infarction at six months (17.6% vs. 17.8%, $p = \text{NS}$) and death at one year (7.6% vs. 7.3%, $p = \text{NS}$) compared with those treated with unfractionated heparin.

Mehta et al. (132) reported results of a pilot study evaluating use of intravenous fondaparinux in 350 patients during elective or urgent PCI. The incidence of total bleeding was similar in patients treated with either fondaparinux or heparin (6.4% vs. 7.7%, $p = 0.61$), as was the composite efficacy end point. Further studies with this novel antithrombin agent are being planned.

Conclusions. The year 2005 yielded dramatic advances in the scientific body of evidence for interventional cardiology. The Innovations in Intervention (I2) steering committee has selected the ten most important published studies of 2005 (Table 3). As expected, trials of mechanical reperfusion and the comparative efficacy of DES dominate the list. In addition, periprocedural pharmacotherapy is a crucial line of investigation. We have had a preview of 2006 with the Late Breaking Trials that were presented in 2005. More detailed information on stem cell therapy is likely. Much more information on DES platforms, especially large, “real-

Table 3. Top-Ten “Must-Read” Published Studies in Interventional Cardiology in 2005

Acronym	Title
ARMYDA-2 (127)	Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty
BRAVE-2 (8)	Bavarian Reperfusion Alternatives Evaluation-2
CAPITAL-AMI (3)	Combined Angioplasty and Pharmacological Intervention versus Thrombolysis Alone in Acute Myocardial Infarction
EMERALD (22)	Enhanced Myocardial Efficacy and Removal by Aspiration of Liberated Debris
FIRSTLINE-AMI (28)	Front-Integrated Revascularization and Stem Cell Liberation in Evolving Acute Myocardial Infarction by Granulocyte Colony-Stimulating Factor
ICTUS (40)	Invasive versus Conservative Treatment in Unstable Coronary Syndromes
PROMISE (23)	Protection Devices in PCI Treatment of Myocardial Infarction for Salvage of Endangered Myocardium
REACT (2)	Rescue Angioplasty versus conservative Treatment or Repeat Thrombolysis
SIRTAX (65)*	Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization
TAXUS-V (85)	Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease

*Winner of the I2 Scientific Achievement award as the most impactful study in interventional cardiology in 2005.

world" registries will be forthcoming. Early, small randomized trials of DES versus CABG may appear, but the large pivotal trials are still at least three years away. More carotid stent registries will be published, but the pivotal CREST trial is still far from completion. Finally, 2006 will likely witness the start of a robust literature in percutaneous valve therapy. Please stay tuned!

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